

# Comparison of ePTFE graft repair with primary suturing in an experimental duodenal perforation model in rats

## Sıçanlarda deneysel duodenal perforasyon modelinde ePTFE greft ile primer dikişin karşılaştırılması

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### BACKGROUND

In this experimental study, we treated peptic ulcer perforation in the first portion of the duodenum using an ePTFE (expanded polytetrafluoroethylene) soft tissue graft and compared results with primary suturing.

### METHODS

Wistar Albino rats were randomized into two groups. A duodenal defect of 3 mm was created in the first portion of the duodenum in all 24 rats. Macroscopic evaluation was done to determine presence of intraabdominal leakage, peritonitis, intraabdominal adhesions, and the level of adhesion, if present. The adhesion severity scoring system was used to score severity of adhesions. Histology section score criteria were used for scoring in microscopic evaluation.

### RESULTS

There was no statistically significant difference between the two groups in the adhesion severity scoring according to grades. However, when overall scoring was considered, a statistically significant difference was determined between the two groups ( $p=0.045$ ). According to microscopic examination, there was no statistically significant difference between the two groups when classified into none to minimal cell accumulation, thin immature granulations and moderately thick granulation ( $p=0.089$ ,  $p=0.178$ ,  $p=0.755$ ); however, there was a statistically significant difference between the two groups in the thick vascular granulation class ( $p=0.005$ ).

### CONCLUSION

Use of the ePTFE graft method is easy, and results are comparable to those achieved with primary suturing. However, our results need further confirmation with larger series in animals and also with human studies.

**Key Words:** ePTFE graft; peptic ulcer; perforation; primary suture.

### AMAÇ

Bu deneysel çalışmada, duodenum birinci kısımda oluşturulan peptik ülser perforasyonu tedavisinde “*expanded polytetrafluoroethylene*” (ePTFE) greft ile primer dikiş yöntemleri makroskopik ve mikroskopik olarak karşılaştırıldı.

### GEREÇ VE YÖNTEM

Wistar Albino sıçanlar rastgele her grupta 12’şer tane olacak şekilde iki gruba ayrıldı. Tüm deneklerde duodenum birinci kısım ön yüzünde 3 mm çapında, tüm duodenum çapının %50’sini geçmeyecek şekilde duodenal perforasyon oluşturuldu. Makroskopik olarak batın içi kaçak, peritonit varlığı ve karın içi adezyonlar değerlendirildi. Adezyonun şiddetini değerlendirmek için adezyon şiddeti skorlama sistemi kullanıldı. Histolojik preparat skorlama ölçütleri mikroskopik değerlendirme için kullanıldı.

### BULGULAR

Her iki grubun adezyon şiddeti skorlamasının istatistiksel analizinde anlamlı fark saptanmadı. Ancak, gruplar bir bütün olarak değerlendirildiğinde adezyon şiddeti skorlaması anlamlıydı ( $p=0,045$ ). Mikroskopik değerlendirmenin istatistiksel analizinde “*none to minimal cell accumulation, thin immature granulation, moderately thick granulation*” olarak sınıflandırılan gruplarda primer dikiş ve ePTFE arasında anlamlı fark bulunmadı ( $p=0,089$ ,  $p=0,178$ ,  $p=0,755$ ). Ancak, “*thick vascular granulation*” olarak sınıflandırılan grupta anlamlı fark bulundu ( $p=0,005$ ).

### SONUÇ

ePTFE greft uygulanması kolay, güvenilir ve sonuçları primer dikişe benzer bir tekniktir. Ancak, bizim çalışmamızdaki sonuçların daha büyük deneysel serilerde ve insan çalışmalarlarıyla desteklenmesi gerekmektedir.

**Anahtar Sözcükler:** ePTFE greft; peptik ülser; perforasyon; primer dikiş.

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Peptic ulcer is a pathology occurring due to an imbalance between offending and defending factors, and its possible serious complications necessitate medical or surgical treatment. Peptic ulcer disease has been associated with many etiological factors such as *Helicobacter pylori* infection, non-steroidal anti-inflammatory drug (NSAID) use, stress, cigarette smoking, diet, and genetics, but multifactorial hypotheses are widely accepted. Complications of peptic ulcer include bleeding, obstruction and perforation. Perforated peptic ulcer is a common surgical emergency and a major cause of death in elderly patients.<sup>[1,2]</sup> Peptic ulcer perforation is the second most frequent abdominal perforation that requires surgery, following perforated appendicitis. Duodenal ulcer perforation is 15 times as frequent as gastric ulcer perforation and is more common in males.<sup>[3]</sup> Although there is a decrease in the requirement for surgical treatment for peptic ulcer due to H2-receptor blocker and proton pump inhibitor usage, a considerable decrease in the incidence of peptic ulcer perforations has not been seen. Peptic ulcer perforation is a life-threatening complication. Treatment of duodenal ulcer perforation generally requires surgery.<sup>[4]</sup> Primary suturing and omental patch (Graham patch) has emerged as the most accepted procedure recently. It is reported that all duodenal perforations and 80-85% of traumatic duodenal injuries may be safely treated with primary suturing.<sup>[5]</sup>

The type of urgent surgery due to peptic ulcer complications may change depending on complication type, preoperative evaluation of the patient, concomitant medical problems, interval between symptom onset and hospital admission, and intraoperative findings. An appropriately chosen surgical procedure decreases the morbidity and mortality.<sup>[6,7]</sup> Along with the many surgical treatment options for peptic perforation such as primary suturing, or the more radical operations such as resection, new treatment options including repair with synthetic grafts or minimally invasive procedures have been developed recently and used.<sup>[8-11]</sup> ePTFE (expanded polytetrafluoroethylene) is an inert biomaterial that does not allow the passage of secretions. It has pores of 10-20 micrometers through which fibrocollagenous tissues penetrate. In one study, Bauer et al.<sup>[12]</sup> observed no gross interference of the ePTFE grafts with fistulization and intestinal obstruction. Although it was reported to be resistant to infections, in some trials ePTFE was found inappropriate for use in contaminated wounds due to detachment risk because of infection.

<sup>[13,14]</sup> The purpose of this study was to compare the results of primary suturing versus with those of ePTFE grafting in an experimental peptic ulcer perforation model in rats.

## MATERIALS AND METHODS

This experimental study was carried out at Ege University Medical Faculty Experimental Surgical Study Laboratory in Izmir, Turkey. The Animal Studies Ethical Committee approved the study. Twenty-four Wistar Albino female rats were used. Rats weighed 150-160 g and were eight weeks old.

Rats were randomized into two groups as primary suturing or ePTFE group. Randomization of the rats and allocation concealment were done by the researchers. Rats were lightly anesthetized with ether. General anesthesia was then induced with 20 mg/kg intramuscular ketamine (Ketalar-Eczacibasi Drug Industries; Turkey). After sterile dressing of the abdominal region with povidone iodine, the abdominal cavity was reached with a median incision of 3 cm, crossing skin, subdermal tissues and fascias.

An anterior incision of 3 mm in the circumference not exceeding 50% of the diameter of the first portion of the duodenum including all duodenal layers was done, causing a perforation opening from the gastrointestinal system to the abdominal cavity. Foreign bodies and gastric secretions around the perforation area were mechanically cleaned.

The perforation area was sutured primarily (simple closure without omental patch) with 4/0 atraumatic silk suture material in the first group, while in the second group, it was closed with ePTFE graft (Gore-Tex; Arizona, USA) (4 mm in radius) by 4/0 prolene suturing (Fig. 1).



**Fig. 1.** Intraoperative appearance of a duodenal defect repaired with ePTFE graft.

**Table 1.** Scoring of histology sections

Score	Histology Sections Score Criteria
1-3	None to minimal cell accumulation. No granulation tissue or epithelial migration.
4-6	Thin, immature granulation that is dominated by inflammatory cells but has few fibroblasts, capillaries or collagen deposition. Minimal epithelial migration.
7-9	Moderately thick granulation tissue, can range from being dominated by inflammatory cells to more fibroblasts and collagen deposition. Extensive neovascularization. Epithelium can range from minimal to moderate migration.
10-12	Thick, vascular granulation tissue dominated by fibroblasts and extensive collagen deposition. Epithelium partially to completely covering the wound.

**Table 2.** Severity of adhesion scoring

Score	Severity of Adhesions
Grade 0	No adhesion
Grade 1	Firm avascular adhesion
Grade 2	Vascular adhesion
Grade 3	Cord-like fibrous adhesion
Grade 4	Plain fibrous adhesion

The abdominal wall was sutured primarily with 4/0 atraumatic silk continually. Oral feeding was started on the 1st postoperative day, and standard feeding was continued thereafter.

All rats were sacrificed under general anesthesia on the 15th postoperative day. The abdominal cavity was opened after sterilization with povidone iodine. Macroscopic adhesion was rated first. Data collection and macroscopic examination were done by the researchers, and microscopic examination was done by pathologist, and all were blinded to the group assignments. For microscopic examination, the liver, stomach and duodenum were excised en bloc from all rats and placed into 10% formaldehyde solutions. Primary suture areas and duodenum tissues around grafts were excised in the Pathology Department. Samples were fixed with 10% formaldehyde solutions and embedded in paraffin blocks. Histological sections 3 mm in thickness were taken. Sections were stained with hematoxylin and eosin. All pathologic specimens were examined by two independent pathologists.

Histology section score criteria were used for scoring in histological evaluation (Table 1).<sup>[15]</sup> No healing tissue was scored as 1 and complete epithelization was scored as 12, and each section was scored according to this scoring system. This histological scoring was done according to the presence or absence of cellular invasion, granulation tissue formation, vascularity, and re-epithelization.

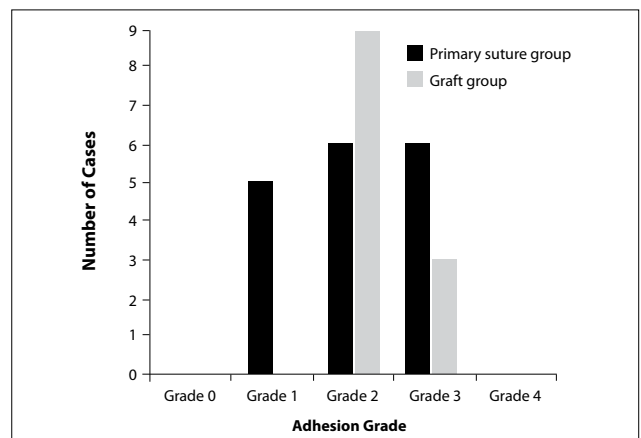
Macroscopic evaluation was done to determine the presence of intraabdominal leakage, peritonitis, intraabdominal adhesions, and the level of adhesion, if present. Adhesion severity scoring system was used to score severity of adhesions (Table 2).<sup>[16-18]</sup>

Mann-Whitney U test was used for statistical analysis. All statistical analyses were done using SPSS 11 for Windows program with a safety interval of 95%. Values of  $p \leq 0.05$  were considered statistically significant.

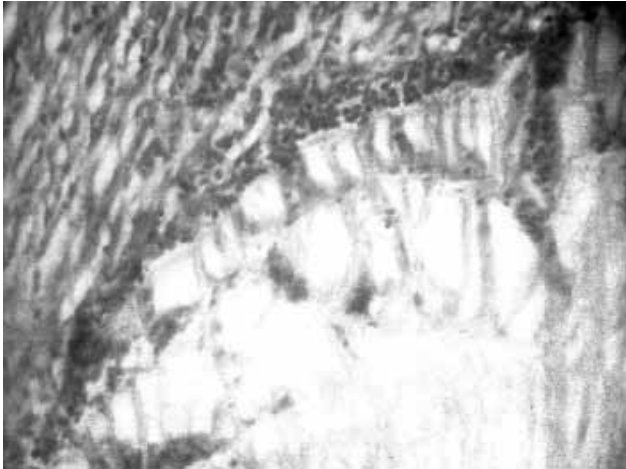
## RESULTS

None of the rats in either group showed any sign of intraabdominal leakage or peritonitis. Adhesion severity scoring results are shown in Fig 2. In the primary suture group, in tissue samples from the suture region, there was a mixed type of inflammatory cell infiltration containing both neutrophils and eosinophils. Inflammatory infiltration severity was medium; only three rats showed high neutrophil concentration and microabscess areas consisting of neutrophilic remnants and necrobiosis.

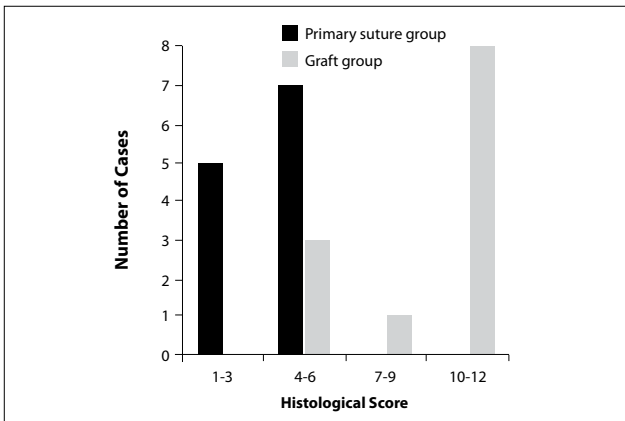
In a few rats, mixed type inflammatory cell infiltration was seen in the serosal layer and in these



**Fig. 2.** Comparison of adhesion severity scoring in the two groups.



**Fig. 3.** Inflammatory cell infiltration containing microabscess areas and basophilic-staining degenerated cellular protein matrix (H-E x 200).



**Fig. 4.** Comparison of histological scoring of the two groups.



**Fig. 5.** Postoperative appearance of Grade 3 adhesion in an ePTFE group rat.

rats a few young fibroblasts, angiogenesis, and loose immature connective tissue formation and collagen deposition were seen.

In the ePTFE grafting group, in tissue samples from the defected region, there was a mixed type and medium severity inflammatory cell infiltration containing eosinophils and neutrophils (Fig. 3). In the majority of the ePTFE group, foreign body type giant cell formation was seen. Furthermore, a dense granulation tissue consisting mostly of fibroblasts and neovascularization containing inflammatory cell infiltration and dense fibroblastic proliferation were seen.

In a few rats, there was a loose connective tissue containing mostly inflammatory cells and fewer young fibroblasts. In 50% of the rats, microabscess areas containing necrobiotic changes were seen, and in the ePTFE materials in these rats, dark basophilic staining degenerated acellular protein matrix was seen. Details of findings are shown in Fig 4.

In the statistical analysis of adhesion severity scoring, there was no statistically significant difference between the two groups according to Grade 1 ( $p=0.089$ ), Grade 2 ( $p=0.319$ ) and Grade 3 ( $p=0.511$ ) (Fig. 5). However, when adhesion severity scoring was considered overall, the difference between the two groups reached statistical significance (Table 3).

In microscopic examination, no statistically significant differences between the two groups were determined when classified into none to minimal cell accumulation, thin immature granulations and moderately thick granulation ( $p=0.089$ ,  $p=0.178$ ,  $p=0.755$ ), but there was a statistically significant difference between the two groups in thick vascular granulation class ( $p=0.005$ ) (Table 3).

## DISCUSSION

Peptic ulcer perforation is a common surgical emergency and a major cause of death in elderly patients.<sup>[1,2]</sup> There is, however, disagreement as to the relative merits of nonoperative treatment, simple closure, or a definitive acid-reduction procedure for perforated peptic ulcers. Nonoperative treatment of perforated peptic ulcers was shown to be effective.<sup>[19]</sup> However, the uncertainty in diagnosis, the potential delay in treatment in nonresponders, and the unreliable response in elderly patients complicate its application in all clinical situations. Although there has been a decline in peptic ulcer incidence due to usage of H<sub>2</sub>-receptor blockers and proton pump in-

**Table 3.** Results of statistical analysis of the two groups

		Mann-Whitney U Test			
		Group	N	Mean Rank	p
Adhesion Scores	Grade 1	Primary sutures	5	15	0.089 (NS)
		ePTFE graft	-	10	
	Grade 2	Primary sutures	6	11	0.319 (NS)
		ePTFE graft	9	14	
	Grade 3	Primary sutures	1	11.5	0.514 (NS)
		ePTFE graft	3	13.5	
	Total	Primary sutures	12	9.625	<b>0.045 (S)</b>
		ePTFE graft	12	15.375	

		Mann-Whitney U Test			
		Group	N	Mean Rank	p
Histological Scores	No granulation	Primary sutures	5	15	0.089 (NS)
		ePTFE graft	-	10	
	Immature granulation	Primary sutures	7	15	0.178 (NS)
		ePTFE graft	3	11	
	Moderately thick gran.	Primary sutures	-	12	0.755 (NS)
		ePTFE graft	1	13	
	Thick vascular granulation	Primary sutures	-	9	<b>0.005 (S)</b>
		ePTFE graft	8	17	
Total	Primary sutures	12	7	<b>&lt;0.001 (S)</b>	
	ePTFE graft	12	18		

NS: Nonsignificant; S: Significant.

hibitors and improvements in endoscopic diagnostic and treatment modalities, recent medical trials do not show a significant decrease in peptic ulcer complications.<sup>[20,21]</sup>

Approximately 75 to 85% of all duodenal injuries can be safely repaired with primary repair or duodenorrhaphy.<sup>[5]</sup> However, primary closure of a large defect (50% of the circumference) may narrow the lumen of the bowel or result in undue tension and subsequent suture line breakdown.

Different surgical, laparoscopic and endoscopic treatment modalities such as repair with omentum, fibrin spray with omental occlusion, occlusion with ligamentum teres hepatis, occlusion with gelatin sponge and fibrin, occlusion with synthetic grafts, and combination of endoluminal and endocavitary endoscopy have been used recently.<sup>[9,10]</sup> Delay in treating a large perforation will lead to severe inflammation, resulting in fragile and indurated sur-

rounding tissue, making it difficult to repair the defect with omental patch closure, falciform ligament patch closure, or closure by pushing an omental plug into the digestive tract with a combined laparoscopic-endoscopic method.<sup>[11]</sup> Although a gelatin sponge plug can be tailored to suit individual cases, it is not ideal for the repair of a large perforation.

Minimally invasive surgical procedures are not limited to only cholecystectomy operations and now involve a variety of surgical procedures including oncologic surgeries. Although the advantages of laparoscopic surgery for patients are well known, leakage from the perforation area is reported in 2-5% of the cases.<sup>[11]</sup> In recent studies, it has been reported that endoscopic/laparoscopic surgical techniques are completely effective and safer when compared with open surgical techniques due to shorter operation duration and fewer complications.<sup>[22,23]</sup> In a recent study, it has been reported that laparoscopic treatment of perforated gastroduodenal ulcer is a simple and safe

procedure with low morbidity when performed by experienced surgeons.<sup>[24]</sup>

Repair with grafts in peptic ulcer perforation is a method currently being tried. In treatment of gastric and intestinal defects, lyophilized dura, teflon, dacron and expanded PTFE grafts have been used in experimental studies and found to be successful.<sup>[25-28]</sup>

ePTFE is an inert biomaterial and impermeable to secretions. The advantages of polytetrafluoroethylene are that they are resistant to chemical attack, lightweight, not brittle, inexpensive, and adaptable, and cause minimal tissue reaction.<sup>[12]</sup> ePTFE has been reported for use in complete rectal prolapse, repair of large abdominal and thoracic wall defects, uterine rupture, repair of gastric defects, and in some vascular procedures. It has also been used in repair of whole thickness defects of the gastrointestinal and biliary tract and found to be successful.<sup>[12,29-35]</sup>

In an experimental study, ePTFE graft was used in the repair of large duodenal defects and the graft was found to be covered with mucosa six months later. As a result, this method was found to be safe and easily performable, but the investigators reported that further experimental studies were required prior to its application in humans.<sup>[32]</sup>

In another experimental study, the authors found the ePTFE graft to be superior to primary suturing, and there was no difference in results between Roux-en-Y duodenojejunostomy and jejunal serosal patch. As a result, they said that ePTFE can be used in the repair of large duodenal defects but that it should not be the first choice.<sup>[8]</sup>

We did not find any macroscopic finding suggesting intraabdominal leakage or peritonitis in either group in our study. This result is consistent with the results of previous studies in the literature.<sup>[8,33-36]</sup>

Increase in fibroblastic activity and fibroblast migration is mostly seen in the proliferation phase of the healing process. Increased fibroblastic activity indicates an early start to the healing process and thus earlier epithelization.<sup>[37]</sup>

In the microscopic evaluation in our study, we found a statistically significant difference between the primary suturing group and ePTFE group in thick vascular granulation class ( $p=0.005$ ). This suggests that wound healing started earlier and stronger in the ePTFE group.

Although the adhesion score was higher in the

macroscopic examination, there was no statistically significant difference between the two groups in intraabdominal leakage and peritonitis. In the microscopic evaluation, thick vascular granulation was statistically significantly higher in the ePTFE group. Because our study represents early stages of the wound healing and consists of dense fibroblast migration and collagen deposition, it is reasonable to find a higher adhesion score in the ePTFE grafting group in the early stages.

An important limitation of our study is the lack of long-term results. Although the high granulation tissue formation rate in the ePTFE group indicates a high adhesion score, we can also conclude that it reflects better wound healing because the primary aim in duodenal perforation treatment is to provide healing without leakage, which is catastrophic. The most important sign of tissue healing is cellular migration and fibrosis. In our study, the graft provided a high degree of cellular migration and granulation tissue formation, meaning the graft is capable of providing strong wound healing tissue. The problem in this issue is that adhesions may cause intestinal obstruction in the long-term; we believe this should be an issue of future larger clinical trials aiming at long-term results.

In conclusion, we have performed a preliminary study of a new method that can be used as an alternative to primary suturing in duodenal ulcer perforation. Histopathological results appear promising for grafting in duodenal ulcer perforation, but further studies are required. In parallel to technical progresses, the increasing quality of grafts, their durability and inert structure seem promising. Our results need further confirmation with larger clinical series before application of the graft in humans.

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